TWO COMPONENT MOLDED VALVE STEMS

Field

The present invention relates to valve stems for metered dose dispensing valves for dispensing metered volumes of a pressurized aerosol formulation, in particular medicinal aerosol formulations, from an aerosol container.

Background

Metering valves are particularly useful for administering medicinal formulations that include a liquefied gas propellant and are delivered to a patient in an aerosol for inhalation, nasal, or sublingual administration.

Medicinal aerosol formulations generally comprise medicament, one or more propellants, (e.g. chlorofluorocarbons and more recently hydrogen-containing fluorocarbons, such as 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA 227)) and possibly excipients, such as surfactant and/or a solvent, such as ethanol.

When administering medicinal formulations, a dose of formulation sufficient to produce the desired physiological response is delivered to the patient. The proper predetermined amount of the formulation must be dispensed to the patient in each successive dose. Thus, any dispensing system must be able to dispense doses of the medicinal formulation accurately and reliably over the shelf life of the medicinal product to help assure the safety and efficacy of the treatment.

Metering dose valves typically comprise an elongate outlet member or valve stem movable between closed and dispensing positions.

The metering valves typically used in commercially available aerosol inhalers, comprise a fixed metering chamber and a valve stem that slides through a diaphragm, also known as an outer stem gasket or seal, mounted in a fixed manner on the valve body of the valve.

However, in some other metering valves, the valve stem may comprise an annular seal capable of forming a fluid-tight seal with a portion of the wall of the chamber or valve body. In particular, one or more annular seals may be arranged onto a portion of the elongate stem element of the valve stem. Examples of such metering valves include various embodiments of shuttle-type metered dose dispensing valves disclosed in US 5,772,085. Other examples include certain embodiments of our co-pending US provisional application 60-408637 filed on September 6, 2002.

Summary of the Invention

It is to be appreciated that in the metering valve of the latter type, i.e. including a valve stem comprising a sealing element, in particular an annular seal, the seal is moving with the valve stem, each and every time the valve stem moves to and from its dispensing position during the operation or firing of the dispensing device. Our co-pending application US 60-408637 discloses the use of processes in which the elongate stem element and the sealing element are co-molded to manufacture the valve stem. The use of such co-molding processes. e.g. multi-shot or multi-component injection molding, for manufacture of valve stems is advantageous for a number of reasons including the provision of a chemical and/or mechanical bond between the respective components, which in turns minimizes the possibility of leakage at the interface of the sealing element and the stem element.

We have now found that the use of polymeric materials comprising a polyaryletherketone (PAEK), a thermotropic liquid crystalline polymer (LCP), a polymethylpentene (PMP) and/or a polyphenylene sulfide (PPS), for the elongate stem element of the valve stem allows the provision of co-molded valve stems having desirably enhanced resistance to mechanical and/or thermal stress and reduced tendency for deformation, e.g. over a typical lifetime-use in a metering valve and/or during the manufacturing process itself. Furthermore, we have found that such valve stems show desirable chemical resistance to aerosol formulation components.

Accordingly, the present invention provides a valve stem for use with a metering valve, the valve stem comprising an elongate stem element and a sealing element arranged onto the elongate stem element, wherein the sealing element is co-molded with at least a portion of the elongate stem element and the elongate stem element is made of a material comprising a polymer selected from the group consisting of polyaryletherketones, thermotropic liquid crystalline polymers, polymethylpentene, polyphenylene sulfide and mixtures thereof.

The present invention provides in addition two methods of manufacturing such a valve stem comprising an elongate stem element and a sealing element. One method can be termed as an over-molding process, while the other is an under-molding process. The former method comprises the steps of:

a) providing a first mold shape;

b) molding a first material comprising a polymer selected from the group consisting of polyaryletherketones, thermotropic liquid crystalline polymers, polymethylpentene, polyphenylene sulfide and mixtures thereof to form the elongate stem element;

c) providing a second mold shape containing at least in part the elongate stem element; and

d) molding a second material to form the sealing element, such that the sealing element is arranged onto and co-molded with at least a portion of the elongate stem element.

Th second, under-molding, method comprises the steps of:

a) providing a second mold shape;

b) molding a second material to form the sealing element;

c) providing a first mold shape underlying at least in part the sealing element; and

d) molding a first material comprising a polymer selected from the group consisting of polyaryletherketones, thermotropic liquid crystalline polymers, polymethylpentene, polyphenylene sulfide and mixtures thereof to form the elongate stem element having the sealing element arranged onto and co-molded with at least a portion of said elongate stem element.

Due to their desirable structural qualities, the valve stems in accordance with the invention are particular suitable for use in metered dose valves and metered dose dispensers, e.g. metered dose inhalers, for the delivery of medicament, e.g. medicinal aerosol formulations. In particular it has been found that embodiments of the valve stem show advantageous, enhanced chemical resistance and/or stability to dimensional change in regard to medicinal aerosol formulations comprising liquefied propellant HFA 134a and/or HFA 227, as well as such formulations comprising additionally ethanol.

Accordingly in further aspects, the invention provides a metered dose valve comprising such a valve stem as well as a metered dose dispenser comprising a container equipped with such a metered dose valve.

The dependent claims define further embodiments of the invention.

The invention, its embodiments and further advantages will be described in the following with reference to the following drawings.

Brief Description of the Drawings

Figures 1a and b represent vertical cross sections through a shuttle-type metered dose valve including a valve stem comprising an elongate stem element and a sealing element.

Detailed Description

It is to be understood that the present invention covers all combinations of particular and preferred aspects of the invention described herein.

For a better understanding of the present invention, an exemplary dispensing valve, which may advantageously include a valve stem in accordance with the present invention, will be initially described.

Figures 1a and b illustrate an exemplary shuttle-type metered dose dispensing valve, disclosed in US 5,772,085 and incorporated herein by reference. Referring to Fig. 1a and b, the valve (15) typically comprises a body (2) having an annular gasket seal (4) for engaging the neck of an aerosol container or vial (not shown) to facilitate a gas-tight seal. The body (2) may be secured to the aerosol container or vial by any suitable means e.g. a conventional outer casing or ferrule (5), which is crimped around the neck of the aerosol container. As can be best seen in Fig. 1b, the body (2) defines a chamber (6) having an outlet passage (10) for dispensing e.g. pressurized medicinal aerosol formulation. The valve stem (13) comprising an elongate stem element (12) extends through the chamber (6) and is movable between a closed or priming position (as shown in Fig. 1a) and a dispensing position (as shown in Fig. 1b). The elongate stem element (12) is provided with two sealing elements, an inner seal (16) and outer seal (18), desirably in the form of annular seals, which provide gas-tight seals between the valve stem and the inner wall of the chamber (6). The chamber (6), external dimensions of the valve stem (13) and the positions of the seals (16 and 18) are arranged to define a pre-determined volume within the chamber (6) between the seals (16 and 18). This can be best understood by reference to Fig. 1b showing the valve in its dispensing position. As can be seen in Fig. 1a, in its closed or priming position the space between the seals (16 and 18) around the valve stem (13) extends into the reservoir containing aerosol formulation. As the valve stem (13) moves downwardly to its dispensing position, the seal (18) moves down the chamber allowing free access of the aerosol formulation into the chamber (6). Further movement of the valve stem causes seal (16) to enter the chamber (6) thereby trapping a metered volume of aerosol formulation between the seals (16 and 18) and the interior wall of the chamber (6). When the valve stem reaches its dispensing position the seal (18) passes outlet passage (10) thereby allowing direct communication between the metered volume and the outlet passage (10) thereby allowing the metered volume of formulation to be dispensed. In the illustrated valve, the valve is arranged, in particular the cross-sectional area of the seals (16 and 18) is arranged, such that the valve stem will be biased outwardly towards its dispensing position by vapor pressure generated by pressurized aerosol formulation contained within the container of the dispenser. The alignment of the valve stem may be ensured by ribs (20), which do not obstruct the free flow of aerosol formulation (as

depicted by the arrow in Figure 1a) around the valve stem (13) between the seals (16 and 18).

It is to be understood that Figures 1a and b show one exemplary dispensing valve, which may comprise a valve stem in accordance with the present invention, and that other dispensing valves, in particular other metered dose dispensing valves, having a valve stem comprising an elongate stem element and at least one sealing element arranged onto the elongate stem element, may also desirably include a valve stem in accordance with the present invention. Further examples of appropriate metered dose dispensing valves are described in our co-pending US 60-408637 application; the contents of which are incorporated herein by reference.

In valve stems in accordance with the present invention, the elongate stem element is made of a material comprising a polymer selected from the group consisting of polyaryletherketones (PAEKs), thermotropic liquid crystalline polymers (LCPs), polymethylpentene (PMP) and polyphenylene sulfide (PPS) and mixtures thereof.

The material may include typical fillers, such as fibers (e.g. glass, mineral or carbon fibers), minerals (e.g. $CaCO_3$), graphite or carbon, which may further enhance structural robustness. PPS-containing materials desirably incorporate fillers, e.g. made of glassfiber, while PAEK-, LCP-, and PMP-containing materials are desirably free of fillers.

Suitable PAEK polymers include polyetherketone, polyetheretherketone, polyetheretherketoneketone, polyetherketoneetherketoneketone and polyetherketoneketone; polyetheretherketone is preferred.

Suitable LCPs include main-chain or side-chain LCPs, more particular comprising rigid-rod-like macromolecules. Suitable polymer classes of LCPs include e.g. polyamides, polyesters and polycarbonates as well as polypeptides, polyoxamides, polyhydrazide, polyazomethine, polyisocyanide, polyisocyanate, polyorganophosphazine, metal-polyine and cellulose derivate, such as ethylcellulose and hydroxypropylcellulose. Preferred LCPs

are copolyesters, copolyamides and polyester-amides, while LCPs comprising linear ester or ester/amide bonds are more preferred.

For use in valve stems in valves for delivery of medicament, the PAEK-, LCP-, PMP- and PPS-polymer is desirably non-toxic and/or recognized for use in medicinal products. Suitable grades for application in valve stems for metering dose valves for the delivery of medicament include for example non-filled polyetheretherketones PEEK™ 381G and 450G (available through Victrex, Lancashire, UK); non-filled and mineral-filled polyester-based LCPs VECTRA™ A950 and A530, respectively (available through Ticona, Kelsterbach, Germany); non-filled PMP TPX™ RT18 (available through Mitsui Chemicals, Düsseldorf, Germany) ; and glassfiber-filled PPS, FORTRON™ 9140L4 and 9140L6 (also available through Ticona).

PAEK, LCP and PMP polymers are preferred, while PAEK and LCP polymers are more preferred and PAEK polymers are most preferred.

The sealing element is arranged onto the elongate stem element and co-molded with at least a portion of the elongate stem element. Under the term "the sealing element is co-molded with at least a portion of the elongate stem element" is to be understood that the sealing element is chemical and/or mechanical bonded to at least a portion of the elongate stem element as the result of a co-molding process used in the manufacture of the valve stem.

Co-molding processes are known in the art, including for example so-called multi-shot or multi-component injection molding. One preferred method of manufacturing a valve stem in accordance with the invention comprises the steps of:

a) providing a first mold shape;

b) molding a first material comprising a polymer selected from the group consisting of polyaryletherketones, thermotropic liquid crystalline polymers, polymethylpentenes and polyphenylene sulfides and mixtures thereof to form an elongate stem element;

c) providing a second mold shape containing at least in part the elongate stem element; and

d) molding a second material to form a sealing element arranged onto and co-molded with at least a portion of the elongate stem element.

Because the sealing element is molded over the elongate stem element, this method can be described as an "over-molding" method.

An alternative, preferred method for manufacturing a valve stem in accordance with the invention is a method of "under-molding", wherein the sealing element is first molded and then subsequently the elongate stem element is molded. This method of manufacturing a valve stem in accordance with the invention comprises the steps of:

a) providing a second mold shape;

b) molding a second material to form a sealing element;

c) providing a first mold shape underlying at least in part the sealing element; and

d) molding a first material comprising a polymer selected from the group consisting of polyaryletherketones, thermotropic liquid crystalline polymers, polymethylpentene, polyphenylene sulfide and mixtures thereof to form an elongate stem element having the sealing element arranged onto and co-molded with at least a portion of said elongate stem element.

For the sake of consistency in the two alternative methods, the wording "first" mold shape and "first" material are used here in connection with steps relating to the molding of the elongate stem element, while the wording "second" mold shape and "second" material are used in connection with steps relating to molding of the sealing element, regardless of the sequential order of the process steps. For molding of the elongate stem element and/or molding of the sealing element the preferred method of molding is injection molding.

It will be appreciated by those skilled in the art that respective mold shapes will be provided as to allow the provision of the particular form of elongate stem element and sealing element needed for the use of the valve stem in the particular dispensing valve. The method may involve a molded component being removed from its mold and then positioned appropriately in another mold form for the molding of the other component.

Alternatively the method may involve a single, repositionable or form-changeable mold, in which upon molding of a component, the mold is re-positioned or changed to provide the appropriate form shape for molding of the other component.

For valve stems comprising two or more sealing elements, those skilled in the art will appreciate that each individual sealing element may be molded simultaneously or sequentially, and that each individual sealing element may have a different form, as needed or desired, and/or may be made of a different material, again as needed or desired.

The sealing element is typically an annular seal. The sealing element is typically elastomeric and may be made of a material comprising a thermoplastic elastomer or a thermoset elastomer.

Various classes of suitable thermoplastic elastomers include polyester rubbers, polyurethane rubbers, ethylene vinyl acetate rubber, styrene butadiene rubber, copolyester thermoplastic elastomers, copolyester ether thermoplastic elastomers, olefinic thermoplastic elastomers, polyester amide thermoplastic elastomers, polyether amide thermoplastic elastomers, copolyamide thermoplastic elastomers and mixtures thereof. Examples of olefinic thermoplastic elastomers are described in WO 92/11190, which is incorporated herein by reference, and include block copolymers of ethylene with monomers selected from but-1-ene, hex-1-ene and oct-1-ene. Other examples of suitable olefinic thermoplastic elastomers are described in WO 99/20664, which is incorporated herein by reference, and in US 5703187 (Dow). Styrene-ethylene-butadiene-styrene copolymers and blends, such as those described in WO 93/22221 and WO 95/03984, both of which are incorporated herein by reference, as well as styrene-ethylene-propylene-styrene copolymers are suitable thermoplastic elastomers. An example of a polyether amide thermoplastic elastomer is PEBAX (Atofina), which is a polyether-block-co-polyamide. Compositions comprising a mixture of inter-dispersed relative hard and relative soft domains may also be employed as suitable thermoplastic elastomers. Examples of such mixture compositions include SANTOPRENE (Advanced Elastomer Systems) which has thermoset EPDM dispersed in a polyolefin matrix or ESTANE (Noveon) which is a polymer of segmented polyester urethanes with a mixture of

crystalline and rubbery nanophases. Other mixtures include olefinic thermoplastic/rubber blends and polyvinyl chloride/rubber blends. Other possibilities include single-phase melt-processable rubbers and ionomers.

Due to the desirable structural properties of the valve stems, in particular the elongate stem element thereof, in regard to resistance to thermal stress and deformation the valve stems are particularly advantageous in allowing the provision of such valve stems comprising co-molded sealing elements made of materials comprising thermoset elastomers.

Preferred thermoset elastomers include thermoset ethylene-propylene-diene terpolymer (EPDM), acrylonitrile-butadiene copolymer (Nitrile rubber), isobutylene-isoprene copolymer (Butyl rubber), halogenated isobutylene-isoprene copolymer (in particular Chlorobutyl rubber and Bromobutyl rubber), polychloroprene (Neoprene), and mixtures thereof, with EPDM, nitrile rubber and butyl rubber being more preferred, EPDM and nitrile rubber even more preferred and EPDM most preferred.

Combinations of co-molded sealing elements made of materials comprising thermoset EPDM, nitrile rubber, butyl rubber, chlorobutyl rubber, bromobutyl rubber and/or neoprene, in particular EPDM, with elongate stem elements made of materials comprising a PAEK, LCP, PPS and/or PMP polymer provide valve stems having particularly advantageous properties in regard to mechanical and/or chemical stress resistance in dispensing valves (e.g. metered dose dispensing valves) for delivery of medicinal aerosol formulations. It is to be understood that each of the possible 24 sealing element/elongate stem element material combinations is individually disclosed here. Valve stems comprising elongate stem elements made of materials comprising PAEK, more particularly polyetheretherketone, and co-molded sealing element(s) made of materials comprising thermoset EPDM show superior structural and/or chemical properties towards medicinal aerosol formulations, in particular medicinal aerosol formulations comprising liquefied propellant HFA 134a and/or HFA 227, more particularly such formulations comprising additionally ethanol.

Referring to the preferred methods for manufacturing described above, in more preferred methods of manufacturing valve stems which include a sealing element made of a material comprising a thermoset elastomer, the material used in the molding steps, more particularly injection molding steps, for forming seal elements ("the second material") desirably comprises a thermosettable elastomer. A thermosettable elastomer is understood here to mean a material (more particularly an injection moldable material) comprising a polymer molecule having at least one double bond, in particular polymer molecules having alkene groups, more particularly pendant alkene groups, which provides sites across which cross-links can be formed upon a curing process allowing the provision of a thermoset elastomer.

For example, thermosettable elastomers used to provide thermoset EPDM (ethylene-propylene-diene terpolymer) and nitrile rubber (an acrylonitrile-butadiene copolymer) typically comprise a polymerized diene, which provides alkene groups in the polymer for cross-linking. Butyl rubbber is typically made from a polymer comprising polyisobutene with a minor proportion of isoprene to provide alkene groups for cross-linking, while halogenated butyl rubber, e.g. chlorobutyl rubber and bromobutyl rubber, is typically made by halogenation of the respective polymer prior to curing. Halogenation does not result in a loss of unsaturation, and cross-linking is typically achieved using magnesium oxide and/or zinc oxide, preferably zinc oxide, resulting in the elimination of the respective metal halide. Similarly Neoprene is typically cross-linked via the elimination of metal chloride from polychloroprene using magnesium oxide and/or zinc oxide optionally with an alkyl diamine.

More particularly in the "over-molding" method, step d) would desirably include after the step of molding (more particular injection molding) a second material comprising a thermosettable elastomer, the following additional sub-steps of:

i) curing said second material; and

ii) removing said second mold shape.

Although typically it is preferably to perform the curing step prior to removing the mold shape, depending on the particular thermosettable elastomer used it may be possible to performing the curing step after removing the mold shape.

In analogous manner, the "under-molding" method described above would desirably include after the step of molding (more particular injection molding) a second material comprising a thermosettable elastomer, the additional step of curing said second material. This curing step is performed preferably prior to step c), but again depending on the particular thermosettable elastomer used it may be possible to perform the curing step before or after step d) (i.e. molding said first material).

The curing process is desirably performed such that at least a majority of the cross-link bonds is formed. Processes for cross-linking are well known and two common types include sulfur-curing, which typically involves sulfur donor molecules to provide polysulfide bridges, and peroxide curing, in which peroxide molecules provide a source of free radicals allowing alkene or pendant alkene groups to form a bridge. Peroxide curing is typically the preferred method of curing, in order to provide materials from which a minimum of harmful extractables could potentially be leached. In peroxide curing to provide a halogentated butyl rubber, such as chlorobutyl rubber and bromobutyl rubber, a co-vulcanizing agent, such as N,N'-m-phenylene-dimaleimide, is often used to achieve adequate cross-linking. Curing processes typically also involve thermal treating, e.g. heating between 110 and 200°C for a minute or more, allowing at least a majority of the cross-link-bonds to be formed. The optimal curing conditions, curing agents, etc. depend on the particular thermosettable elastomer being molded and possibly also on the overall dimensions, size and/or form of the particular sealing element being molded. In regard to process efficiency, it may be desirable to use higher temperatures over shorter times to achieve rapid turnover through the molding tools.

In both methods after the curing step and the removing of the last mold shape, it may be desirable to perform an additional thermal treatment step, for example to substantially complete cross-linking and/or to optimize physical properties of the thus formed sealing element. This thermal treatment step may involve heating between 110 and 200°C for typically a longer time period than the curing step, e.g. over a time period of 0.5 to 24 hours.

Metered dose dispensing valves comprising a valve stem in accordance with the invention as well as metered dose dispensers comprising a container equipped with such a metered dose valve are particularly advantageous for use in dispensing medicament, in particular medicinal aerosol formulation, due to the desirable properties of the valve stems. The use of valve stems in accordance with the invention in conjunction with medicinal aerosol formulations comprising a medicament and a propellant selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and a mixture thereof, more particular further comprising ethanol, is particularly advantageous.

A preferred metered dose dispensing valve, suitable for dispensing metered volumes of a pressurized aerosol formulation, comprising a valve stem in accordance with the invention, is a valve which further comprises a chamber and an outlet passage, wherein the valve stem extends into the chamber and is movable relative to the chamber between non-dispensing and dispensing positions, the valve stem having a configuration including an external surface and the chamber having an internal configuration including an internal surface such that a movable metered volume of pressurized aerosol formulation is capable of being defined therebetween and such that during the movement between its non-dispensing and dispensing positions the valve stem sequentially:
i) allows free flow of aerosol formulation into and out of the chamber;
ii) defines a closed metered volume for pressurized aerosol formulation between the external surface of the valve stem and internal surface of the chamber, and
iii) moves with the closed metered volume within the chamber without decreasing the volume of the closed metered volume until the metered volume communicates with the outlet passage thereby allowing dispensing of the metered volume of pressurized aerosol formulation. The valve stem desirably comprises a second sealing element, said second sealing element being arranged onto and co-molded with at least a portion of the elongate stem element and being longitudinally spaced from the first sealing element, each sealing element having a sealing surface capable of forming a gas-tight seal with the internal surface of the chamber.